EXHIBIT 13

IN THE UNITED STATES PATENT OFFICE

Application Serial No. 09/567,451

Our Ref.: PT1830000
CUSTOMER NO. 23607

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Title: CHRONOTHERAPEUTIC DILTIAZEM FORMULATIONS AND THE ADMINISTRATION THEREOF

5/a w/att + Formal Drawgs (15 sht)

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Group Art Unit: 1615

Due Date: May 3, 2001

Bet 5-1-01

RESPONSE TO OFFICIAL ACTION OF NOVEMBER 3, 2000 AMENDMENTS AND REMARKS

April 30, 2001

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 South Clark Place
Crystal Plaza 2, Room 1B03
Arlington, Virginia 22202
U.S.A.

Fee processed

Dear Sir:

In response to the outstanding Official Action dated November 3, 2000 and due for response February 3, 2001, Applicant encloses a Request for a three month extension of time with the fee for a large entity of $890.00 U.S. funds making this response due May 3, 2001. If there is any deficiency or surplusage of the fees enclosed for the Extension of Time, please obtain any such deficiency or credit the surplusage to Deposit Account 08-3255 and advise Applicant's Agent.

Applicant encloses a terminal disclaimer filed in order to avoid delay in the prosecution of this application having regard to Application Serial No. 09/465,338. Applicant does not agree with the Examiner in respect of a Terminal Disclaimer being required. Nonetheless, Applicant is forwarding a terminal disclaimer for this application against Application Serial No. 09/465,338 in order not to delay the prosecution of this application. Applicant also encloses the fee of $110.00 U.S. funds to file the enclosed terminal disclaimer. If there is any deficiency or surplusage of the fees enclosed for the terminal disclaimer, please obtain any such deficiency or credit the surplusage to Deposit Account 08-3255 and advise Applicant's Agent.

IN THE DISCLOSURE

No amendment.

IN THE DRAWINGS

Pursuant to the Notice of Draftsperson's Patent Drawing Review, Applicant encloses formalized drawings of Figures 1-10c.

IN THE CLAIMS

Please amend the claims as follows:

1. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.

3. (Amended) A method of treatment of a patient's hypertension and/or angina comprising administration of a preparation of claim 1 [or 2] in the night to a patient for effect the next morning and which formulation exhibits a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given with food and without food according to the same FDA guidelines or criteria.

4. (Amended) The controlled-release Galenical preparation of claim 1 [or 2] wherein the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem
(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours.

5. (Amended) The controlled-release Galenical preparation of claim [1 or] 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours.

6. (Amended) The preparation of claim [1, 2,] 4 [or 5] wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

8. (Amended) The preparation of claim [1, 2, 4, 5,] 6 [or 7] wherein the preparation is a diffusion controlled preparation.

9. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7 or 8] wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

10. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8 or] 9 in capsule form.

11. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8 or] 9 in tablet form.

12. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8,] 9[, 10 or 11] wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

14. (Amended) The preparation of claim 13 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each microgranule [bead], ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

15. (Amended) The preparation of claim [12, 13 or] 14 wherein the membrane comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[])] which hydrates the preparation.

16. (Amended) The preparation of claim 12 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[])] which hydrates the preparation.

17. (Amended) The preparation of claim [12, 13, 14, 15 or] 16 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30D] and hydroxypropylmethylcellulose.

18. (Amended) The preparation of claim 17 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the

membrane to swell while fluid penetrates and hydrates the microgranule [bead], and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

19. (Amended) The preparation of claim 13 [or 14] wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane [Eudragit RS, Eudragit RL] and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

20. (Amended) The preparation of claim [1, 2, 4, 5, 6, 7, 8,] 9[, 10 or 11] wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

21. (Amended) The preparation of claim 20 wherein the dissolution agent is an organic acid comprising [such as] adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid[,] or tartaric acid [and the like] which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgranules pass into the [higher pH] regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

41. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 120 mg of Diltiazem.

42. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 180 mg of Diltiazem.

43. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 17 or 17] wherein the preparation contains 240 mg of Diltiazem.

44. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 300 mg of Diltiazem.

45. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 360 mg of Diltiazem.

46. (Amended) The preparation of claim [1, 2, 4,] 5[, 6, 7, 10, 11, 12, 13, 14, 15, 16 or 17] wherein the preparation contains 420 mg of Diltiazem.

48. (Amended) The preparation of claim [12, 13, 14, 15, 16,] 17[, 18 or 19] wherein the wetting agent is selected from:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose, <u>including</u> [commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.) such as] sucrose stearate [marketed under the trade name of Crodesta];
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene [(Brijs, Renex and Eumulgines, Henkel, RFA)];
sorbitan fatty acid esters [(Span, Atlas, U.S.A.)];
polyglycides-glycerides and polyglycides-alcohols esters [(Gelucires, Gattefosse, France)]
Metal salts [such as NaCl or sodium lauryl sulphate].

49. (Amended) The preparation of claim 12 wherein the wetting agent is in association with the diltiazem in the <u>microgranule</u> [bead] and not mixed

therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [such as Eudragit NE30D] enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

52. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent [The preparation of claim 12, 13, 14, 15, 16, 17, 18, 19, 48 or 49] in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5

(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

54. (Amended) The preparation of claim 12[, 13, 14, 15, 16, 17, 18, 19, 48 or 49] in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid

methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

56. (Amended) The preparation of claim 12[, 13, 14, 15, 16, 17, 18, 19, 48 or 49] in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

58. (Amended) The preparation of claim 12[, 13, 14, 15, 16, 17, 18, 19, 48 or 49] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

59. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

60. (Amended) The controlled-release Galenical preparation of claim [1 or] 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid

methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

63. (Amended) The preparation of claim 60[, 61 or 62] wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

64. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for

providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

[The preparation of claim 60, 61 or 62] wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

65. (Amended) The preparation of claim 60[, 61, 62, 63 or 64] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

66. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 60[, 61, 62, 63, 64 or 65] to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

67. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours.

68. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10

hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours.

69. (Amended) The preparation of claim [67 or] 68 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

70. (Amended) The preparation of claim [67,] 68 [or 69] wherein the Diltiazem is in the form of Diltiazem HCl.

71. (Amended) The preparation of claim [67,] 68[, 69 or 70] wherein the preparation is a diffusion controlled preparation.

72. (Amended) The preparation of claim [67,] 68[, 69, 70 or 71] wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

73. (Amended) The preparation of claim [67,] 68[, 69, 70, 71 or 72] in capsule form.

74. (Amended) The preparation of claim [67,] 68[, 69, 70, 71 or 72] in tablet form.

75. (Amended) The preparation of claim 67[, 68, 69, 70, 71, 72, 73 or 74] wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

77. (Amended) The preparation of claim 76 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each <u>microgranule</u> [bead], ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

78. (Amended) The preparation of claim [75, 76 or] 77 wherein the membrane comprises a water-dispersible or water-soluble polymer [(such as HPMC)] and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[)] which hydrates the preparation.

79. (Amended) The preparation of claim 75 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer [such as Eudragit NE30D (a neutral

copolymer] of acrylic acid ethyl ester and acrylic acid methyl ester[)] which hydrates the preparation.

80. (Amended) The preparation of claim [75, 76,] 77[, 78 or 79] wherein the membrane comprises Eudragit NE30D and hydroxypropylmethylcellulose.

81. (Amended) The preparation of claim 80 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule [bead], and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

82. (Amended) The preparation of claim [76 or] 77 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic polymer [Eudragit RS, Eudragit RL] and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

83. (Amended) The preparation of claim [67,] 68[, 69, 70, 71, 72, 73 or 74] wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

84. (Amended) The preparation of claim 83 wherein the dissolution agent is an organic acid comprising [such as] adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid[,] or tartaric acid [and the like] which permits the diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the [higher pH] regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

103. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 120 mg of Diltiazem.

104. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 180 mg of Diltiazem.

105. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 240 mg of Diltiazem.

106. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 300 mg of Diltiazem.

107. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 360 mg of Diltiazem.

108. (Amended) The preparation of claim [67,] 68[, 69, 70, 73, 74, 75, 77, 78, 79 or 80] wherein the preparation contains 420 mg of Diltiazem.

110. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent. [The preparation of claim 75, 76, 77, 78, 79, 80, 81 or 82] wherein the wetting agent is selected from:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose, commercialized under the name of sucroesters [(Gattefosse, France)] or under the name of crodesters [(Croda, U.K.)] such as sucrose stearate marketed under the trade name of Crodesta;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene [(Brijs, Renex and Eumulgines, Henkel, RFA)];
sorbitan fatty acid esters [(Span, Atlas, U.S.A.)];
polyglycides-glycerides and polyglycides-alcohols esters [(Gelucires, Gattefosse, France)]
Metal salts [such as NaCl or sodium lauryl sulphate].

111. (Amended) The preparation of claim 75 wherein the wetting agent is in association with the diltiazem in the microgranule [bead] and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [such as Eudragit NE30D] enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

114. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent. [The preparation of claim 75, 76, 77, 78, 79, 80, 81, 82, 110 or 111] in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose [(Avicel ph101)]	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester [Eudragit NE30 D] (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

116. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after

administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent. [The preparation of claim 75, 76, 77, 78, 79, 80, 81, 82, 110 or 111] in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

118. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent. [The preparation of claim 75, 76, 77, 78, 79, 80, 81, 82, 110 or 111] in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid

methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

120. (Amended) The preparation of claim [75, 76,] 77[, 78, 79, 80, 81, 82, 110 or 111] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

122. (Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg [or more] of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

125. (Amended) The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester [(such as Eudragit NE30D)], together with suitable adjuvants.

127. (Amended) The preparation of claim 122[,] or 124[, 125 or 126] wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

128. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 122, 123[,] or 124[, 125, 126 or 127] to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Attached hereto as **Exhibit A** is a marked-up version of the changes made to the claims by the present amendment. Exhibit A is entitled "EXHIBIT A - CLAIMS WITH MARKINGS TO SHOW CHANGES".

Attached hereto as **Exhibit B** is a clean set of all pending claims following entry of this amendment. Exhibit B is entitled: "EXHIBIT B - CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT". All of the currently pending claims are consolidated in this list for the convenience of the Examiner.

REMARKS

Claims 1-128, as amended, remain in the application. No new subject matter has been added.

The Examiner has indicated that Claims 52, 64, 114 and 126 would be allowed if written in independent form. This has been done.

The Examiner has rejected the remaining claims on the basis of improper multiple dependency and inclusion of trade marks and trade names and improper expressions in the claims, which objections have been addressed in the revised claims and, in Applicant's respectful submission, overcome, and on the basis of two prior art references, European Patent Application EPO 856313 Geoghegan ('313) and WO 93/00093 Deboeck ('093). The Examiner takes the position that what has been claimed in claims 1-41, 43, 47, 67-103, 105 and 109 is taught under 35 U.S.C. §102 in the '313 application (anticipation) and that all the claims (except those indicated as being allowable) are obvious under 35 U.S.C. §103 from the teachings of '313 or '093.

With respect to '313 the Examiner claims that the broad release rates have been taught in this reference and that the dissolution rates in Applicant's claims are overlapped by the '313 Patent. The Examiner admits, however, that "... EPA '313 does not disclose the exact release rates claimed by applicant..." (bottom of page 8).

Firstly, with respect to claims 1, 2 and 3, there is no basis in '313 or any reference which teaches the limitations in the claims. Therefore, these claims and all claims dependent thereon are allowable.

Further, the determination of the dissolution rates in '313 is in accordance with U.S. Pharmacopoeia XXI in 0.05M KCl at pH 7.0 (not in accordance with Applicant's claimed procedure).

Additionally, Applicant's claims further include a Cmax in the blood plasma at a Tmax of between about 10-15 hours (dependent claims include a Cmax in the blood plasma at a Tmax of between 11-13 hours). Applicant asserts that '313 does not teach Applicant's claimed formulations and methods. In additional support of Applicant's position (see above), Applicant directs the Examiner to example 14 based on example 1 which has a Cmax of 5 hours. (See Figure 2a). Example 14 states the formulation of Example 1 is suitable for once

daily administration given the Tmax of 14 hours (page 20, lines 33-34). However, Figure 2(a) shows otherwise (Tmax of 5 hours).

Further, while the Pharmacological Data appears for a single dose of the Example 4 formulation to give a Cmax at a Tmax of 13 hours (See page 24, line 4 and page 25, line 10), the dissolution rates of the formulation of example 4, Applicant respectfully submits, are different from Applicant's claimed formulations. The actual percentages are different. The Example 4 dissolution described at page 9, is after 2 hours .35% diltiazem is released, after 4 hours 5.10% diltiazem is released. In Applicant's claims (where provided) between about 1% to about 15% is released after two hours and about 7% to about 35% after four hours. Applicant's more restricted claims claim amounts of about 4% to about 8% after two hours and about 16% to about 21% after four hours. Therefore, the '313 application neither teaches nor contemplates Applicant's claimed formulation. Therefore, it cannot constitute a basis for rejection under 35 U.S.C. §102.

The Examiner next asserts Applicant's claims are obvious over '313 stating at page 9,

> "Further, the formulation also releases the drug at the same rate as that claimed by applicant, therefore, it appears that these limitations do not render any unexpected results. It is the position of the examiner that these are limitations which would be routinely determined by one of ordinary skill through minimal experimentation, as being suitable, absent the presentation of some unusual and/or unexpected results. The results must be based on the specific limitations."

Firstly, Applicant has shown that '313 does not teach Applicant's claims and denies the Examiner's statement "...the formulation also releases the drug at the same rate as that claimed by Applicant." as discussed above.

FURTHER SUPPORT

Additionally, Applicant respectfully submits that there is unexpected results by using Applicant's claimed invention. In this regard, the Examiner is referred to the following:

The '313 Application corresponds in whole and in part to a number of United States patents in the same patent family including United States Patent No. 4,917,899; 4,894,240; 4,891,230; 4,721,619; and 5,002,776 (the family of patents listing is enclosed as **Schedule "A"**). Applicant's reasons for bringing this correspondency to the Examiner's attention will become clear from the following:

Cardizem CD is a formulation containing Diltiazem HCl. Among the patents listed in what is known as "the Orange Book" (Approved Drug Products – The products in this list have been approved under Section 505 of the Federal Food, Drug and Cosmetic Act) are three patents filed by Carderm - United States Patent Nos. 5,286,497; 5,439,689 and 5,470,584 (in addition to a number of the Elan patents including United States Patent No. 4,894,240) – an excerpt from the Orange Book and the cover is attached as **Schedule "B"**.

U.S. Patent 5,286,497 issued from U.S. Application 58,534 which was a continuation of Application 872,572 which is a continuation of Application 702,567. U.S. Patent 5,439,689 issued from Application 164,062 which was a continuation of Application 58,534 (Patent 5,286,497). U.S. Patent 5,470,584 issued from Application 394,573 which was a continuation of Application 164,062 (Patent 5,439,689).

Application 702,567 filed May 20, 1991

The broadest claim filed in the application is set out as follows:

1. A diltiazem bead comprising:

a) a central core containing an effective amount of diltiazem or a pharmaceutically acceptable salt thereof, optionally in association with pharmaceutically acceptable excipients, and;

b) a sufficient quantity of a suitable polymeric coating material which substantially envelops said diltiazem core so that said diltiazem bead exhibits the following in vitro dissolution profile

when measured in a type 2 dissolution apparatus (paddle), according to U.S. Pharmacopoeia XXII, at 37°C in 0.1 N HCl at 100rpm:

a) from 0-45% of total diltiazem is released after 6 hours of measurement in said apparatus;

b) from 0-45% of total diltiazem is released after 12 hours of measurement in said apparatus,

c) from 0-75% of total diltiazem is released after 18 hours of measurement in said apparatus, and;

d) not less than 40% is released after 24 hours of measurement.

The Examiner rejected the claims filed under 35 USC §112 as being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention. The Examiner also rejected the application in view of Geoghegan in view of Joshi under 35 USC 103 (obviousness) asserting that:

> Geoghegan, teaches a diltiazem pellet comprising a central core (col. 2, lines 27-50), from 0-45% of total diltiazem is released between 6-12 hours (col. 2, lines 53-54) and from 0-75% of diltiazem is released after 18 hours (col. 2, lines 55-56). While Geoghegan does not teach the use of diltiazem ... beadlets. Joshi, teaches a pharmaceutical composition in the form of beadlets (col. 2, lines 11-14). It would have been obvious to one skilled in the art at the time of the invention to ... combine the teachings of Geoghegan in view of Joshi because Geoghegan, teaches as conventional a novel diltiazem pellet formulation comprising a core of diltiazem surrounded by an multiplicity of sequentially applied and dried layers of a film forming polymer for a controlled absorption rate over a period of time. Joshi, teaches a novel pharmaceutical composition of beadlets which acts as a controlled release formulation.

(Geoghegan is U.S. Patent 4,917,899 and Joshi is U.S. Patent 4,808,413.) – (The Examiner also cited in later actions United States Patent No. 4,894,240.)

An amendment was filed in response to this action wherein Claim 1 was cancelled and Claim 2 was amended as follows:

2. A diltiazem bead comprising:

a) a central core containing an effective amount of diltiazem or a pharmaceutically acceptable salt thereof, optionally in association with pharmaceutically acceptable excipients, and;

b) a sufficient quantity of a suitable polymeric coating material which substantially envelops said diltiazem core so that said diltiazem bead exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle), according to U.S. Pharmacopoeia XXII, at 37°C in 0.1 N HCl at 100rpm:

[A bead according to claim 1 which exhibits the following in vitro dissolution pattern:

a) from 0-15% of total diltiazem is released after 6 hours of measurement in said apparatus;]

b)] a) from 0-15% of total diltiazem is released after 12 hours in said apparatus;

[c)] b) from 0-45% of total diltiazem is released after 18 hours of measurement in said apparatus, and;

[d] c) not less than 45% of total diltiazem is released after 24 hours of measurement in said apparatus.

In making the proposed amendment the applicant submitted in part as follows:

Geoghegan et al is directed to diltiazem pellets suitable for incorporation into a product allowing controlled absorption over a twelve hour period. The USPTO has stated that Geoghegan et al renders claim 2 obvious since it discloses pellets having the following dissolution profiles:

b) from 0-15% of total diltiazem is released between 6-12 hours, and from 0-45% of total diltiazem is released by 18 hours (both at Column 2, lines 54-56). This is factually incorrect and the reference does not disclose any pellets having such a dissolution profile.

The Examiner's attention is directed to column 2, lines 53-56 of Geoghegan et al which discloses pellets having the following profiles that:

a) from 0-25% of the total diltiazem is released after 4 hours of measurement in said apparatus;

b) from 20-45% of the total diltiazem is released after 6 hours of measurement in said apparatus, and;

c) not less that 85% of total diltiazem is released after 13 hours of measurement in said apparatus. The USPTO statements regarding claims 10, 11 and 12 are also factually incorrect.

To insure the accuracy of the record the undersigned would like to point out that the dissolution profiles in Geoghegan et al were conducted in 0.05M KCl at pH7.0, whereas those presented in the instant application are carried out in 0.1N HCl.

(The Examiner should examine the entire file history for all submissions.) In the prosecution, the Applicant also submitted as follows:

The present invention is directed to minimizing the variance between peak and trough levels of diltiazem that have been associated with prior art once-a-day diltiazem formulations such as those encompassed by United States Patent 4,894,240. This is accomplished by utilizing a controlled release formulation containing two types of beads having differing but predetermined release rates. One type of bead is a delayed release bead as described by claims 2-10 in which most of the diltiazem is released from the bead 12 hours to 24 hours after immersion into the test medium. Geoghegan et al would not motivate one of ordinary skill in the art to produce a diltiazem bead in which most of the diltiazem is released 12 hours after immersion into the test medium.

By Official Action dated June 26, 1992 (Paper No. 8) the Examiner again rejected the application stating:

Applicant's arguments filed 4/10/92 have been fully considered but they are not deemed to be persuasive.

The applicant argues that the diltiazem pellets for controlled absorption taught by Geoghegan does not disclosure the dissolution profile of the applicants invention. Furthermore, there is no motivation by Geoghegan to produce a diltiazem bead in which most of the diltiazem is released 12 hours. The examiner does not agree with the applicants arguments since it was already disclosed in the previous office action that Geoghegan, teaches a diltiazem pellet

> which releases from 0 to 25% of total diltiazem after 4 hours, from 20 to 45% after 6 hours and not less than 85% after 13 hours. The profile of Geoghegan reads directly on the claimed invention of the applicant. Joshi, teaches a diltiazem bead in a polymeric coating. One skilled in the art would recognize that the constituent components can be adjusted according to the parameters judged necessary. The examiner does not have to copy every parameter of said claimed invention with the cited references under 35 USC 103 to render said claims obvious. Since Joshi, was not cited for teaching said dissolution profile the applicants argument without merit.
>
> It is the examiners opinion that all of the parameters of the claimed invention have been fully met by the cited references of Geoghegan and Joshi. It would have been prima facie to one skilled in the art that either combined or alone the cited references would motivate one to produce a diltiazem bead with the claimed dissolution profile. The motivation lies in the references of Geoghegan who teaches the use of diltiazem pellets with the claimed dissolution profile.

The Examiner thus concluded that Geoghegan teaches a diltiazem pellet which releases from 0-25% of total diltiazem after 4 hours, from 20-45% after 6 hours, not less than 85% after 13 hours. The profile of Geoghegan, according to the Examiner, reads directly on the claimed invention.

Application 702,567 was abandoned in favour of Application 872,572.

Application 07/872,572

In an Official Action dated 07/20/92 the Examiner relied on Geoghegan '240 (U.S. Patent 4,894,240) together with Stevens stating:

> Geoghegan, teaches a diltiazem bead comprising a central core containing diltiazem (co. 2, lines 21-25), polymeric coating which envelops said diltiazem (col. 2, lines 24-29), with said dissolution profile (col. 2, lines 36-52). While Geoghegan does not teach said specific polymer, Stevens teaches said compositions (col. 1, lines 40-44). It would have been obvious to one skilled in the art at the time of the invention to modify and incorporate the teachings of Geoghegan in view of Stevens because Geoghegan teaches as conventional a novel controlled absorption diltiazem formulations

in pellet/bead forms. Stevens teaches a novel sustained release pharmaceutical compositions which comprises diltiazem.

In claims 2, 10, 11, 12, 13, 14, 15 and 16 Geoghegan teaches a bead exhibiting said vitro dissolution pattern (col. 2, lines 42-51; col. 3, lines 3-15).

The claims were not amended in the response but for a minor amendment. Applicant submitted as follows:

As is discussed in the introduction of the specification, the present invention is directed to a diltiazem formulation which solves the problems associated with prior art once-a-day diltiazem formulations. Diltiazem is subjected to a first-pass effect after administration. This means that a large percentage of the administered dose is metabolized by the liver and rendered inactive before it has had an opportunity to reach the general circulation. Thus, prior art formulations designed to provide zero order release of a drug are inappropriate for diltiazem. The release of a constant amount of diltiazem results in the inactivation of a significant percentage of the administered dose resulting in sub-therapeutic blood levels. It is necessary to use a controlled release formulation with diltiazem. The formulation must release sufficient diltiazem at appropriate times to allow the saturation of the liver's metabolic capacity, so that blood levels of diltiazem can rise significantly to therapeutic levels.

The controlled release formulations of the instant invention provide a release pattern which solves this problem. This formulation is composed of two types of diltiazem beads having differing release rates. One type of diltiazem bead can be characterized as a delayed release diltiazem bead. Minimal diltiazem is released from this bead until 12 hours after immersion into a test medium. The second type of bead is a rapid release bead in which substantially all of the diltiazem is released in the first 8 hours after immersion into the test medium. Claims 2-10 are directed to the delayed release beads and claims 11-16 are directed to formulations containing both types of beads.

The applicant also submitted the following with respect to Geoghegan '240:

Geoghegan #240 is directed to a once-a-day diltiazem formulation. This formulation is designed to produce peak plasma levels of diltiazem 10-14 hours after administration and more preferably from 12-14 hours after administration. This delayed release profile is accomplished by utilizing diltiazem pellets that are coated with a

multi-layered polymeric membrane having a specific dissolution profile. These coated diltiazem pellets are combined with up to 25 w/w% of uncoated diltiazem pellets thereby producing the final formulation.

As noted above, the formulation of the instant invention contains two types of diltiazem pellets, both of which contain polymeric coatings. One type can be characterized as a rapid release pellet. It is designed to release up to 100% of its diltiazem within 6 hours after testing. The second type of bead can be characterized as a delayed release bead and it does not release substantial quantities of diltiazem until 12 hours after testing. Claims 2-10 are directed to only the delayed release pellets and claims 11-16 are directed to the final formulation containing both rapid release beads and delayed release beads.

The USPTO has taken the position that claims 2-16 are obvious since Geoghegan teaches polymeric coated diltiazem pellets having dissolution profiles similar to those instantly claimed, and that Stevens teaches the specific polymers utilized in the instant invention. Thus, the instant invention can be produced by modifying the pellets of Geoghegan with the polymers of Stevens.

It is respectfully submitted that this rejection should be removed because Geoghegan #240 does not teach a dissolution profile similar to that contained in claims 2-16. The release rates of Geoghegan's coated pellets differ substantially from those of the instant invention. The release rates of Geoghegan #240 and those of the instant invention are specified below. The release rates are calculated in differing solvent systems (KC1 vs HCl). Despite the differing solvent systems, the release rates are so divergent as to demonstrate the unobviousness of the instant invention.

Geoghegan #240

POLYMERIC COATED DILTIAZEM PELLETS

Time	% dissolution in KCl
2 hours	0-35%
4 hours	5-45%
8 hours	30-75%
13 hours	60-95%

Invention

RAPID RELEASE PELLETS		DELAYED RELEASE PELLETS	
Time	% Dissolution	Time	% Dissolution
3 hours	0-40	12 hours	0-15

6 hours	30-100	18 hours	0-45
		24 hours	≥45

Geoghegan discloses a diltiazem pellet which releases from 60-95% of its diltiazem within 13 hours of testing. Claims 2-10 are directed to a diltiazem pellet in which no more than 15% of its diltiazem is released during the first 12 hours of testing. In order to arrive at Applicants invention by modifying Geoghegan's pellets, it would necessary to decrease Geoghegan's release rate by a factor of nearly 400% (ie. ≤15% of diltiazem is released vs. ≥60% in a comparable time frame).

the art of record provides no motivation for decreasing Geoghegan's release rate so dramatically. Such a drastic modification can not be considered merely optimization. **The prior art must provide the motivation to make the modifications necessary to arrive at the claimed invention, In re Lalu 223 USPQ 1257 (1984). The art of record provides no such motivation.**

The subject mater of claims 11-14 is directed to a formulation containing the delayed release pellets in combination with the rapid release pellets. To arrive at the claimed subject matter, it would be necessary to make two significant modifications to Geoghegan's coated pellets. To produce the rapid release pellets it would be necessary to increase the dissolution profile for some of Geoghegan's polymeric coated pellets (i.e., up to 100% in 6 hours versus ≥60% in 13 hours). It would also be necessary to decrease the dissolution profile of Geoghegan's remaining pellets by a factor of 400% as described above for the delayed release pellets. It would also be necessary to remove all of the uncoated pellets from Geoghegan's formulation. Neither Geoghegan nor Stevens provides the motivation for producing a formulation containing these two types of polymeric coated diltiazem pellets having the dissolution profiles specified above. Again, such a drastic modification cannot be considered to be merely optimization. Finally, Geoghegan #240 teaches away from the dissolution profile encompassed by claim 2-16. The Examiner's attention is directed to Column 2 of the Geoghegan patent, lines 1-15 and lines 53-61, for the specific passages. Geoghegan #240 teaches that in order to produce a once-a-day diltiazem formulation, it is necessary to achieve peak plasma levels of diltiazem 10-14 hours after administration and more preferably 12-14 hours. Further, formulations producing peak plasma levels of diltiazem 6-9 hours after administration are only suitable for twice-a-day administration.

The Examiner's attention is directed to page 34 of Applicants' specification, Table XI, which outlines the pharmacokinetic profile of the formulation of Example #3. This formulation exhibits a

release rate corresponding to the subject matter of claims 2-16. This Table is reproduced below for the Examiner's convenience:

TABLE XI

Pharmacokinetic Parameter	Oral Solution	Once a Day Capsule
AUC	910.3 ng/mLxhr	849.1 ng/mLxhr
Cmax	78.6 ng/mL	54.4 ng/mL
Trough	19.8 ng/mL	24.7 ng/mL
Ratio	4.7	2.9
Tmax	1.3 hours	7.3 hours
F	1.0	0.93

Examination of this Table shows that the formulation of the instant invention, having the dissolution rates specified above, produced peak plasma levels of diltiazem approximately 7 hours after administration. Geoghegan teaches that such a formulation would not be suitable for once-a-day administration. However, as demonstrated in Table X, this formulation produced therapeutic levels of diltiazem over a 24 hour period. Thus, Geoghegan #240 teaches away from the instant invention rather than suggesting such a formulation.

The Examiner's attention is also directed to page 3, line 30 through page 4, line 27, of Applicants' specification which discusses Geoghegan #240. Applicants have found that the formulation of Geoghegan produced a wide variance between peak and trough plasma levels of diltiazem. The formulations of the instant invention minimizes this variance. (emphasis added)

The Examiner issued a further action on November 10, 1992, once again rejecting the claims and stating:

Applicant's arguments filed 08/14/92 have been fully considered but they are not deemed to be persuasive.

The applicants argue that the cited references of Geoghegan #240 and Stevens does not teach a dissolution profile similar to the claimed invention is without basis or merit. The applicant also argues that the release rates are calculated in different solvent systems (KC1 vs HC1). Despite the differing solvent systems, the release rates are so divergent as to demonstrate the unobviousness of the claimed invention. The examiner finds the applicants argument (absent of a declaration providing the different release rates of KC1 vs HC1) without merit as the release rates of diltiazem pellets with respect to the amount of polymeric coatings for said varying pellets are not persuasive because generally it is obvious to

> the person having ordinary skill in the art to manipulate the proportions of the components to achieve a desired dissolution profile.
>
> Geoghegan teaches a dissolution profile of from 2 to 24 hours not the 13 hours upper limit that the applicant recites from the Geoghegan reference which encompass said vitro dissolution pattern claimed by the applicant. Furthermore, Stevens teaches a sustained release pharmaceutical composition with a controlled dissolution of the active principle over a long period of time and said coating film (the thickness) can be varied. This strongly suggests a coating mixture capable of reading on the dissolution rates as claimed by the applicant and does not read away from the claimed invention. The test for combining references is what the combination of disclosures take as a whole would suggest to one of ordinary skill in the art. In re Simon, 174 USPQ 114 (CCPA 1972); In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). Suggestion of the claimed invention in any or all of the references but what the references taken collectively would suggest.
>
> It is the examiners opinion that all of the parameters of said claimed invention have been fully met by the combined cited references disclosed. The applicant is reminded that the provisions under 35 USC 103 does not make it mandatory to read on every single parameter of said claims. It would be prima facie obvious to one of ordinary skill in the art to modify and combine the teachings of Geoghegan in view of Stevens. The motivation lies in the controlled and sustained release of Diltiazem with said claimed polymeric coatings with said dissolution profiles. (emphasis added)

Application 08/058,534

Applicant next filed this application as a continuation application together with a preliminary amendment enclosing a number of declarations. The applicant reiterated the grounds for rejection by the Examiner and stated:

> In response thereto, the enclosed declarations provide information concerning the different release rates of KCl vs. HCl. More importantly, they demonstrate that in clinical studies, representing actual use situations, the claimed invention **provides an entirely different release rate from the Elan formulations which are the subject of the Geoghegan '242 patent**. In addition, it is **submitted that the clinical studies demonstrate new and unexpected results for the claimed composition vis-à-vis the two Elan formulations. Such**

evidence of new and unexpected results is believed sufficient to rebut any prima facie case of obviousness which may be said to exist (the actual existence which is denied) with the combination of Geoghegan '242 and Stevens.

The applicant, for the first time, with evidence, claimed that its invention provided an entirely different release rate from the Elan formulations which are the subject to the Geoghegan #242 (*sic*) patent. In this regard, the declaration by Diane L. Peterson is enclosed in **Schedule "C"**. The declaration of V.J. Bhargava also enclosed with **Schedule "C"** discussed blood plasma samples and, after reviewing the attached declaration of Dr. Weir (also enclosed in **Schedule "C"**), it was Dr. Bhargava's opinion that the present invention is superior to those described by the '240 patent. The reason for this superiority is based upon the substantially higher trough levels provided by the formulation of the instant invention when compared with that obtained by the Elan formulations. He then continued:

The trough level is the plasma concentration of drug that is achieved by a given formulation immediately prior to the scheduled administration of the next dose. A good sustained release product provides trough plasma concentrations that may be comparable to those obtained when the product may be given in divided doses 3 to 4 times a day. If this quality is lacking the patient may be achieving sub-therapeutic trough levels and may lack efficacy over part of the dosing period.

The trough levels obtained with the two Elan formulations, the 60mg tablets administered 4 times daily and the formulation of the instant invention are presented immediately below for the Examiner's convenience:

MEAN TROUGH LEVELS

TREATMENT	TROUGH LEVEL ng/ml
Elan A	48.5
Elan B	46.0
60 mg qid	67.3
Invention	66.5

levels produced by the two Elan formulations are approximately 30% below that produced by the formulation of the instant invention. The significantly lower level of drug may correspond to

a decreased therapeutic effect over the relevant portion of the dosing period.

Another advantage of the formulation of the instant invention is how closely the trough levels correspond to those obtained with the 60mg tablets administered 4 times daily. This will facilitate the conversion of the patient from a dosage form requiring administration 4 times daily to the convenience of a once a day dosage form.

The final declaration was that of Scott Weir, also enclosed with **Schedule "C"**, describing how the '240 diltiazem formulations made by the Elan patent were obtained from Elan Corporation plc which identified the formulation and which gave the release profiles:

The dissolution profiles of each of these formulations was evaluated in 0.05M KCL as described in the '240 patent beginning at line 65, column 2. This dissolution testing was carried out at Elan's facilities by Elan personnel and the results were provided to MMD.

Elan formulation A exhibited the following dissolution profile:

DISSOLUTION PROFILE

TIME	% DILTIAZEM HCl RELEASED
2 Hr	12.2
4 Hr	18.1
6 Hr	34.2
8 Hr	50.8
10 Hr	64.4
13 Hr	79.7
24 Hr	97.6

Elan formulation B exhibited the following dissolution profile:

DISSOLUTION PROFILE

TIME	% DILTIAZEM HCl RELEASED
2 Hr	14.7
4 Hr	21.5
6 Hr	36.9
8 Hr	53.8
10 Hr	69.0
13 Hr	82.5
24 Hr	102.2

Pharmacokinetic profiles of the two Elan formulations were determined in a study and blood plasma samples were drawn from the volunteers identified at page 4. The diltiazem mean plasma concentrations for the two formulations are set out at pages 5 and 6 as follows:

TABLE I ELAN FORMULATION A

Time	Diltiazem Mean Plasma Concentration (ng/ml) (% CV)	
6th Dose:		
0 hours	49.31	(31.28%)
7th dose		
0 hours	48.62	(31.02%)
2 hours	75.04	(36.64%)
4 hours	65.89	(37.53%)
6 hours	63.92	(36.31%)
7 hours	71.32	(37.11%)
10 hours	98.14	(27.59%)
12 hours	104.24	(25.86%)
14 hours	95.92	(26.10%)
16 hours	84.99	(23.44%)
18 hours	75.94	(25.34%)
20 hours	61.89	(23.78%)
22 hours	53.34	(25.37%)
24 hours	47.70	(25.85%)
30 hours	28.50	(30.07%)

TABLE II ELAN FORMULATION B

Time 6th Dose:	Diltiazem Mean Plasma Concentration (ng/ml) (% CV)	
0 hours	47.73	(36.84%)
7th dose		
0 hours	47.15	(33.84%)
2 hours	94.52	(27.55%)
4 hours	77.13	(31.83%)
6 hours	69.78	(33.79%)
7 hours	70.15	(31.41%)
10 hours	91.36	(29.85%)
12 hours	94.97	(29.27%)
14 hours	84.36	(25.43%)
16 hours	78.47	(27.43%)
18 hours	69.00	(25.20%)
20 hours	56.63	(26.07%)
22 hours	48.57	(25.20%)
24 hours	43.05	(24.63%)
30 hours	27.75	(37.10%)

TABLE III Cardizem Tablets

Time	Diltiazem Mean Plasma Concentration (ng/ml) (% CV)	
21st Dose:		
0 hour	71.31	(28.42%)
25th dose		
0 hour	66.47	(30.79%)
1 hour	86.19	(29.73%)
2 hours	107.98	(27.01%)
3 hours	127.01	(24.28%)
4 hours	108.94	(26.40%)
6 hours	73.11	(25.60%)
26th dose		
1 hour	82.15	(25.82%)
2 hours	105.69	(28.46%)
3 hours	110.13	(23.39%)
4 hours	94.10	(21.72%)
6 hours	61.90	(26.95%)
27th dose		
1 hour	58.29	(30.48%)
2 hours	79.66	(28.42%)
3 hours	93.11	(26.33%)
4 hours	77.48	(25.04%)
6 hours	55.05	(24.25%)
28th dose		
1 hour	60.26	(37.97%)
2 hours	64.96	(36.89%)
3 hours	70.69	(31.47%)
4 hours	73.61	(26.37%)
6 hours	64.19	(25.97%)
12 hours	24.94	(33.39%)

With further information given and Table III with respect to the Cardizem tablets after the 21st dose, 25th dose, 26th dose, 27th dose and 28th dose. At page 6, Table IV provides trough- average of 7 a.m. plasma concentrations obtained prior to dosing on day 6 and 7 in addition to 24 hours post-dose and H8 are given together with other data.

The Mean values for the following pharmacokinetic parameters were determined from the plasma diltiazem concentration time profiles: AUC-Area under the curve, Cmax - Maximum steady-state plasma concentration, Trough - average of 7 AM plasma

concentrations obtained prior to dosing on days 6 and 7 in addition to 24 hours post-dose on day 8, Ratio- ratio of C-max to C-min, the minimum steady state plasma concentration, Tmax - time to maximum concentration. These mean values are reported below in Table IV (Value in parenthesis represents % CV).

TABLE IV

	Tablet 60 mg qid	Elan A 240 mg/ day	Elan B 240 mg/day
AUC (0-24 hr) (ng/mixhr)	1960 (23)	1801 (26)	1760 (26)
CMAX (ng/ml)	129 (23)	108 (26)	106 (27)
RATIO (CMAX/CMIN)	2.8 (17)	2.5 (20)	2.6 (15)
TMAX (hr)	4.0 (57)	11.8 (22)	8.1 (62)
TROUGH (ng/ml)	67.3 (26)	48.5 (27)	46.0 (29)

The applicant in a further response enclosing revised claims, thanked Examiner Page for the interview and made the following submissions (also made at the interview):

During that interview, it was explained that the assignee of the present invention, Carderm, is a recent spin-off of Marion Merrell Dow Inc., which has for years sold diltiazem HCl under the trademark Cardizem. The once-a-day form of Cardizem, then, is sold under the trademark Cardizem CD. Enclosed is a copy of the advertising literature concerning Cardizem CD, which literature was shown to Examiner Page during the interview. The once-a-day diltiazem formulation sold under the trademark Cardizem CD is the subject matter of the present application. Examiner Page was also shown one of the Cardizem CD capsules and it was explained that that capsule contained a blend of A) rapid release diltiazem beads and B) delayed release diltiazem beads. Dr. Bhargava explained that because diltiazem has a relatively short half life and because it absorbs throughout the gastrointestinal track, it has been found that a "stair-step release profile" for the once-a-day formulation is highly desirable.

That is, when compared to Geoghegan Patent No. 4,894,240, which is the principal reference relied upon by the Examiner in this case, there is a considerable difference in the drug release mechanism

involved. In the Geoghegan patent, the coated drug has a coating which is a mixture of a water insoluble and water soluble material. Upon dissolution of the water soluble material, the coating on the drug becomes porous and the drug is gradually released steadily over a period of time. In the Geoghegan formulation, some free drug (uncoated) is also blended with that coated drug in order to obtain some immediate release of the drug. The net result is a release curve which rises rapidly and then gradually tapers off.

On the other hand, as Dr. Bhargava explained, the release profile for Cardizem CD is a "stair-step" one. That is demonstrated by the Bhargava and Weir declarations, which were previously submitted in this case and by the Peterson declaration which was shown to Examiner Page and which is enclosed herewith. Note, as shown in the Peterson declaration, that at 13 hours the blended formulation of the present invention has a release of 33.9%; whereas, in Geoghegan Patent No. 4,894,240, the release after 13 hours is 60-95%. That is, the blended diltiazem formulation of the present invention has a "flat step" of the "stair-step release profile" at around 13 hours. Such a release profile is not shown in the art of record, as recognized by Examiner Page. That is, in the Examiner Interview Summary Record, it is stated: "Claim 11 represents the invention of a mixture of distinctly coated beads in a formulation having a specific dissolution profile. Claims presented define over the prior art of record."

... patentable subject matter in the combination of previous claim 11 (which covers the blend of rapid release coated diltiazem beads and delayed release coated diltiazem beads as specified) and the specific dissolution profile of the blend (which was previously the subject matter of dependent claim 15), new independent claim 17 is presented herewith. Claim 17 is essentially a combination of previously pending claims 2, 11, and 15. As Examiner Page requested, it sets forth the blend of rapid release coated diltiazem beads having a specific profile, and delayed release coated diltiazem beads having a specific profile; with the blend, then, having the specific release profile set forth. Claims 18-29 depend from independent claim 17. All other claims have been canceled.

The case was allowed. The claims issued in U.S. Patent 5,286,497 (which the Examiner can review).

Application 08/164,062

This application was filed as a continuation and subsequently issued as U.S. Patent 5,439,689.

The Examiner allowed the claims. The Examiner stated in his reasons for allowing the case:

> The following is an Examiner's Statement of Reasons for Allowance: The optimized blood levels of diltiazem over a 24 hour period is accomplished by a controlled release dosage form which exhibits a release profile wherein decreasing the variance between peak and trough levels of diltiazem is not taught or suggested by the prior art of record.

Therefore the optimized blood levels for the diltiazem from the formulation provides a decrease in the variance between peak and trough levels of diltiazem of the prior art which was not taught or suggested by the prior art of record.

Application 394,573

A preliminary amendment was filed by which the pending claims were cancelled and new claims were inserted. These claims, however, only claimed a delayed release diltiazem formulation.

The Examiner rejected these claims based on the obviousness type double patenting having regard to U.S. Patent 5,286,497 and required a terminal disclaimer. A terminal disclaimer was filed and the patent issued.

Further with respect to the formulations claimed in the claims of U.S. Patent 5,470,584 although relating to a delayed release formulation, the claimed subject matter was nevertheless found to be the same invention as U.S. Patent 5,286,497 and therefore a terminal disclaimer had to be made. The release from the delayed release components for both was the same and provided a maximum release at 18 hours of 75%. All of the claimed formulations of the three patents gave, according to the Examiner, a decrease in the variance between the peak and troughs of the blood plasma levels.

Applicant encloses data in **Schedule "D"** which, in Applicant's respectful submission, substantiate that its claimed formulation provides unexpected results over '313. Table 1 compares Cardizem CD, which was found by Examiner Page to exhibit a release profile wherein decreasing the variance between peak and trough levels of diltiazem was not taught or suggested by the prior art of record with Applicant's formulation. In Table 1, Cardizem CD exhibited 106.85% variance. Applicant's claimed invention (Diltiazem HCl ER capsules) exhibited 84.98% variance. Therefore, Applicant's claimed invention exhibits at least the same decreasing variance as Carderm CD and therefore exhibits "unexpected results" which the Examiner stated was lacking. Thus, in Applicant's respectful submission, Applicant's claimed invention is meritorious, inventive and allowable. There is no motivation in '313 to make Applicant's claimed formulations. '313 does not teach Applicant's benefits. ('313 does not even mention the limitations of claims 1, 2 and 3.)

Applicant also encloses in further support, as **Schedule "E"**, an article by Eradiri, O. et al., entitled "Comparison of diltiazem bioavailability from 3 marketed extended-release products for once-daily administration: implications of chronopharmacokinetics and dynamics", International Journal of Clinical Pharmacology and Therapeutics, (1997), Vol. 35, No. 9, p. 369-373. This article shows at page 372 the degree of fluctuation of Cardizem CD (134±40%) and Tiazac (139±36%) – Tiazac will be discussed with respect to Deboeck ('093).

The '093 Patent Application

The Examiner has also rejected the claimed invention in view of '093 under 35 U.S.C. §103(a). In doing so, the Examiner admits that '093, "does not teach the exact rates of release as claimed by Applicant, nor do they discuss the rates of release after 8 hours, nor do they disclose all the specific amounts of the above-mentioned ingredients." The Examiner however takes the position that '093 does teach overlapping release rates and while '093 does not teach a Cmax at 10-15 hours (Tmax) as claimed by Application, the claims are obvious. Firstly, there is no teaching at all of the subject matter of Claims 1, 2 or 3. Therefore,

these claims and all dependant claims are allowable in Applicant's respectful submission. Secondly, the broad release rates of '093 at page 4, lines 24-34 are not those in Applicant's claims. The examples at page 5, lines 16-20, page 14, lines 16-21 and page 15, lines 9-13 (Example 4) are not within Applicant's claimed ranges. Nor is the Cmax of '093 between about 10-15 hours (Tmax). Figure 1 shows a Tmax at 8-9 hours. Figure 1 shows a steady state plasma level after 7 days administration of the Example 4 dosage (see page 15, lines 15-31). Figure 2 appears to have a Cmax at Tmax of 10-11 hours. However, Example 4 does not have a release profile within Applicant's claimed release profiles. Despite these differences, the Examiner still maintains obviousness stating "Applicant's invention is not patentably distinct from the prior art.

Applicant respectfully further responds to this ground of rejection as follows:

WO 93/00093 (Deboeck) corresponds to United States Patent No. 5,529,791 and United States Patent No. 5,288,505 (see the Family of Patent listing enclosed as **Schedule "F"**). United States Patent No. 5,529,791 is identified as relating to Tiazac in the Orange Book extract enclosed as **Schedule "B"** herein. As discussed in **Schedule "E"**, Tiazac has a fluctuation of (139±36%), a greater fluctuation (even at its best reading) than with respect to **Schedule "D"** (which compares a formulation using Applicant's claimed invention and Cardizem CD). The Examiner's attention is also directed to Figure 8 of the application which graphically illustrates the differences in Tiazac and formulations in accordance with this application. There is, once again, no motivation to make Applicant's claimed formulation in '093. '093 does not teach Applicant's benefits.

In view of the above submissions, Applicant submits that all claims herein are inventive over the prior art provide unexpected utility over all prior art and Applicant respectfully requests allowance of same.

Applicants have enclosed one cheque in the sum of $1,000.00 U.S. which incorporates the fee of $890.00 U.S. for the three month extension of time and

$110.00 U.S. for the terminal disclaimer. If there should occur an overpayment or an underpayment of fees in respect of this submission, the Commissioner is authorized to access Deposit Account Number 08-3255 to make the appropriate adjustments and advise Applicant's agent.

If the Examiner has any questions, she is respectfully requested to contact Applicant's agent, Ivor M. Hughes, at area code 905-771-6414, collect at the Examiner's convenience. After the Examiner has examined the response and material, should the Examiner not find all the claims allowable, or if the Examiner requires further material from Applicant, she is respectfully requested to contact Ivor Hughes to arrange for an interview with Applicant's agents and representatives.

Respectfully submitted,

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for Ivor M. Hughes
Registration No. 27,759
Agent for the Applicant

IMH*kdk
Enclosures
1. Requisition for 3 Month Extension of Time
2. Terminal Disclaimer
3. Cheque for $1,000.00 U.S.
4. Formalized Drawings of Figures 1-10c
5. Exhibit A
6. Exhibit B
7. Schedule "A" (family of patents listing)
8. Schedule "B" (excerpt from the Orange Book and the cover)
9. Schedule "C" (declarations by Diane L. Peterson, V.J. Bhargava and Scott Weir)
10. Schedule "D" (data)
11. Schedule "E" (an article by Eradiri, O. et al., entitled "Comparison of diltiazem bioavailability from 3 marketed extended-release products for once-daily administration: implications of chronopharmacokinetics and dynamics", International Journal of Clinical Pharmacology and Therapeutics, (1997), Vol. 35, No. 9, p. 369-373)
12. Schedule "F" (Family of Patent listing)